

Comment Number	Guideline Document Paragraph (§)	Comments
1	3	Minor suggested edits.
2	4 and 5	<p>The statement that has been made during the expert consultation of this draft guideline that there are actually no false negatives if one also considers all available reference data (including human data) is not necessarily supported by the available data. It has been asserted that the false negative substances (when compared to rabbit skin test data) are non-irritants in humans. However, it should be noted that each of these substances actually produced irritation in at least 20% (6/29 or 6/30) of the human volunteers. Jirova et al. (2007) concluded that these substances do not pose “significant acute skin irritation potential” because each substance produced irritation in fewer individuals than did the positive control substance, 20% sodium dodecyl sulfate (SDS, also SLS). However, di-n-propyl disulfide had 6/30 positive reactions (22/30 with SLS) and 2-isopropyl-2-isobutyl-1,3-dimethoxypropane had 6/29 positive reactions (26/29 with SLS). Furthermore, 2/6 individuals with positive reactions to di-n-propyl disulfide had a severity score of 2, indicating a moderate reaction, and one of these individuals had moderate scabbing at the application site (Kandarova, personal communication), indicative of a potential corrosive effect. The relative importance of human and animal data should be carefully considered, as summarized in the OSHA Hazard Communication Standard, which states that: “...positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience but require an assessment of the robustness, quality and statistical power of both human and animal data.” (see <i>Federal Register</i> Vol. 74, No. 188, section A.0.3.3, page 50443).</p> <p>Additionally, according to the available rabbit skin test data and using in vivo scores <math>\geq 2.3</math> as the threshold for an irritant response (i.e., as per the GHS), 13 irritant compounds were included in the SIVS validation database. Of these, 2 compounds, di-n-propyl disulfide and 2-isopropyl-2-isobutyl-1,3-dimethoxypropane, were false negative in the in vitro test methods [15% (2/23)]. It should be noted that the <i>in vivo</i> rabbit erythema scores for di-n-propyl disulfide and 2-isopropyl-2-isobutyl-1,3-dimethoxypropane were 3.0/4.0 (moderate to severe erythema) and 4.0 /4.0 (severe erythema to eschar formation preventing grading of erythema) respectively. These significant in vivo lesions should not be discounted. Therefore, users need to be aware of the possibility that, based on the validation database, false negative results can occur when using these in vitro assays. Accordingly, we have proposed additional text to be added to paragraphs 4</p>

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		and 5 of the TG, which are included in the <b>Attached Tracked Document</b> .
3	7	A continued concern from the USA is the possibility that the 12-21% false negatives generated by in vitro corrosivity test methods (15 different substances were identified by one or more of the in vitro corrosivity test methods as noncorrosive in one or more tests during the validation studies) may not be detected in the in vitro irritation test methods (i.e., resulting in a corrosive substance being unlabelled for dermal hazard). While one might conclude that using the sequential decision strategy set forth in OECD TG404, (e.g., QSAR, measuring pH, etc.) might correct these results, (e.g., any chemical with a pH extreme is considered a corrosive), it is unlikely that this could completely resolve this problem. For example, the identity of the substance being tested may be unknown such that QSAR analyses are not feasible. Additionally, many corrosives with a pH extreme are not corrosive, and routine use of such a classification criterion to eliminate false negative corrosives would therefore not likely be acceptable to industry, considering the increased cost of packaging and transport for substances erroneously labeled as corrosives. Furthermore, many corrosive substances do not have a pH in these extreme ranges, and this criterion still might not avoid false negatives. It should also be emphasized that there should be standardized methods provided for proper measurement of pH and associated buffering capacities. NICEATM is in the process of completing a study to evaluate these false negative substances, with results expected by May 2010. Due to the uncertain ability of the in vitro skin irritation test methods to identify false negative in vivo corrosives, additional text has been recommended for inclusion in paragraph 7 in order to identify the potential shortcoming of a purely in vitro testing strategy (i.e., when the only available information is derived from the in vitro corrosivity and irritation test methods) ( <b>see Attached Tracked Document</b> ).
4	7	Because of the potential limitations of these test method, it is unlikely that they could be considered as complete replacements for skin corrosivity and irritation testing as outlined in TG 404. Therefore, it is important that this point be recognized in the test guideline.

[illegible]